II. REMARKS

A. Regarding the § 112, second paragraph, rejections

Claims 40 and 56 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Applicants respectfully traverse the rejections.

Claim 40 is alleged to be indefinite for reciting the phrase "homologous to the coding region, nucleotides 594 to 2198, of SEQ ID NO:43, as shown in SEQ ID NO:45." To make the subject matter of claim 40 clearer, Applicants have amended the claim to recite homology to "nucleotides 594 to 2198 of SEQ ID NO:43."

As an aside, the Action alleges that it is not clear "how these claims further limit the claims from which they depend." Applicants are puzzled about this allegation, as there are no claims dependent upon claim 40.

Claim 56 is alleged to be indefinite because it is unclear how the recited host cell expresses purified recombinant heparanase. In response, Applicants have amended claim 56 to require that the recited host cell includes the fragment of claim 32. The amendment is supported in the specification, for example, at page 40, lines 1-3, which discloses that the host cell can include the nucleic acid of the invention.

In view of these amendments, withdrawal of these rejections is respectfully requested.

B. Regarding the § 112, first paragraph, rejection

Claims 32, 36, 38, 40, 41, 45, 47 to 49, 53, 55 and 56 to 59 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. Applicants respectfully traverse the rejection.

More specifically, the Action alleges that the specification does not establish regions of the heparanase protein which may be modified, the general tolerance of heparanase to modification and a scheme for modifying amino acid residues of heparanase with the expectation of retaining activity.

In response, Applicants submit a declaration from Dr. Iris Pecker, a named inventor of the subject application. The declaration shows that the specification does provide more than sufficient guidance to enable the skilled artisan to practice the invention as currently claimed.

In particular, Dr. Pecker analyzed the alignment data shown in Figure 17 of the subject application. In her opinion, it provides ample guidance to the skilled artisan on how to make active heparanase variants. For example, residues 77 to 98 of mouse heparanase (SEQ ID NO:44) are identical to the corresponding residues of the variants shown in Figure 17. By contrast, for example, residues 15 to 28 have 11 residue differences. Similarly, comparing mouse and human heparanase, residues 129 to 138 (referring to the reside positions in human), for example, have 9 of 10 differences at this region. With such guidance, the skilled artisan would know to not vary residues 77 to 98 and to vary one or more residues among residues 15 to 28 and/or 129 to 138, especially with a similar amino acid residue substitution (e.g., hydrophilic). The skilled artisan could even further use the guidance of the subject specification to replace one or more amino acid residues in SEQ ID NO:44, especially in these highly variable regions, with those corresponding residues found in human or rat heparanase. See declaration, para. 2.

Looking at heparanase protein more broadly, residues 49 to 109 (referring to human) make up 61 residues. Comparing mouse and human region in this region, there are only 10 of 61 changes. Comparing mouse and rat in this region, there are only 6 of 61 changes. This is therefore a very conserved region, one that the skilled artisan would likely not vary, at least as a starting point, in trying to obtain additional heparanase homologs. Declaration, para. 3.

Indeed, the conserved region of residues 49 to 109 was confirmed to be the 8 kDa unit of active heparanase. By contrast, variable regions 15 to 28 and 129 to 138, discussed in paragraph 2 above, are not part of either the small or large units of mature heparanase. Declaration, para. 4.

Moreover, Figure 19 of the subject application provides even further guidance. Figure 19 shows the secondary structure prediction for heparanase using computer assistance. The portions depicted as "H" are helical, and the portions depicted as "E" are extended beta strand structures. Declaration, para. 5. Still further, the glutamic acid residue of heparanase, predicted as the proton donor, is marked with an asterisk in Figure 19. Given the relative location of the proton donor and the predicted secondary structure of the protein, the glutamic acid residue that functions as the nucleophile is most likely at position 343 or 396 (see underlined residues in Figure 19, and page 105, lines 20-22 of the subject specification). Declaration, para. 6.

Given the wealth of information in the subject specification, the skilled artisan can make heparanase variants without undue experimentation. Declaration, para. 7.

Applicants respectfully point out that the Examiner has acknowledged enablement of amino acid sequences that have 95% homology with human heparanase (see Office Actions issued by Examiner Hutson in U.S. App. Ser. No. 09/776,874). And this admission by the Examiner was made less guidance than found in the subject application. More specifically, the subject application adds the information found in Figure 19 and page 105, as cited above and analyzed in paragraphs 5 and 6 of the attached declaration.

For all of these reasons, Applicants respectfully request that this rejection be withdrawn.

III. CONCLUSION

All of the issues raised in the Office Action have been addressed and are believed to have been overcome. Accordingly, it is respectfully submitted that all the claims under examination in the subject application are allowable. Therefore Applicants respectfully request a Notice of Allowance to this effect.

Respectfully submitted,

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